Neuroendocrine Tumors (NETs) of the Minor Papilla/Ampulla

Analysis of 16 Cases Underlines Homology With Major Ampulla NETs and Differences From Extra-Ampullary Duodenal NETs

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Abstract: Neuroendocrine tumors (NETs) of the minor papilla/ampulla (MIPA) are rare and poorly studied. Only individual case reports and no comprehensive analysis are available from the literature. We collected 16 MIPA NETs and investigated their clinicopathologic and immunohistochemical features, including markers such as somatostatin, pancreatic polypeptide, gastrin, serotonin, MUC1, cytokeratin 7, and somatostatin receptors type 2A and 5. The median age at diagnosis was 57.5 years, and the female-to-male ratio was 2.2:1. The median NET size was 1.45 cm, and most (94%) were low-grade (G1) tumors. Similarly to what was observed in the major ampulla, 3 histotypes were found: (i) ampullary-type somatostatin-producing tumors (ASTs, 10 cases), characterized by somatostatin expression in most tumor cells, focal-to-extensive tubulo-acinar structures, often with psammoma bodies, MUC1 reactivity, and no or rare membranous reactivity for somatostatin receptor type 2A; (ii) gangliocytic paragangliomas (3 cases), characterized by the coexistence of 3 tumor cell types: epithelioid, often reactive for pancreatic polypeptide, ganglion-like cells, and S100 reactive sustentacular/stromal cells; and (iii) ordinary nonfunctioning NETs (3 cases), resembling those more commonly observed in the extra-ampullary duodenum. Comparable histotypes could also be recognized among the 30 MIPA NETs from the literature. No NET-related patient death among MIPA cases was observed during a median follow-up of 38 months; however, MIPA ASTs showed lymph node metastases and invasion of the duodenal muscularis propria or beyond in 44% and 40% of cases, respectively. In conclusion, MIPA NETs closely resemble tumors arising in the major ampulla, with predominance of ASTs.

Key Words: ampullary-type somatostatin producing tumor, gangliocytic paraganglioma, MUC1, nonfunctioning neuroendocrine tumor, somatostatin receptor

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TABLE 1. Clinicopathologic and Outcome Data of the 16 MIPA-NETs Cases Investigated

Case	Age (y)	Sex	Concomitant Neoplasms	Treatment	Mitoses/ 2 mm^2	Ki67 (%)	WHO Grade	LVI	Tumor Size (cm)	Level of Invasion	T	Lymph Node Metastasis	AJCC Stage	Status at Last Follow-up (mo)
#1	73	M	No	Pancreaticoduodenectomy	0	1	1	Yes	0.6	Duodenal submucosa	2	No	II	Dead for other causes (2)
#2	47	M	No	Transduodenal tumor excision	0	2	1	No	2.5	Duodenal submucosa	2	No	II	Alive (275)
#3	57	M	No	Pancreaticoduodenectomy	1	2	1	Yes	2.5	Duodenal submucosa	2	Yes	III	Alive (72)
#4	66	F	No	Pancreaticoduodenectomy	0	1	1	No	1.3	Subserosa	3	No	II	Alive (86)
#5	44	F	No	Pancreaticoduodenectomy	0	1	1	Yes	1.3	Muscularis propria	2	Yes	III	Alive (75)
#6	58	F	No	Pancreaticoduodenectomy	2	2	2	Yes	2	Duodenal submucosa	2	Yes	III	Alive (50)
#7	51	F	No	Pancreaticoduodenectomy	0	2	1	No	1.5	Duodenal submucosa	2	No	II	Alive (3)
#8	69	F	Pancreatic ductal adenocarcinoma	Pancreaticoduodenectomy	0	1	1	No	0.2	Intrasphincteric	1	No	I	Alive (28)
#9	59	F	Pancreatic ductal adenocarcinoma	Pancreaticoduodenectomy	0	1	1	No	0.6	Intrasphincteric	1	No	I	Alive (14)
#10	31	F	Major ampulla NET, pheochromocytoma	Pancreaticoduodenectomy	0	2	1	Yes	1.7	Pancreatic parenchyma	3	Yes*	III*	Alive (10)
#11	46	F	No	Pancreaticoduodenectomy	1	1	1	Yes	1.5	Muscularis propria	2	Yes	III	Alive (22)
#12	51	M	No	Transduodenal tumor excision	0	2	1	No	2.5	Muscularis propria	2	No	II	Alive (166)
#13	64	F	No	Minor ampullectomy	0	0.5	1	No	1.5	Muscularis propria	2	No	II	Alive (134)
#14	70	M	No	Transduodenal tumor excision	0	0.4	1	Yes	0.7	Duodenal submucosa	2	No	II	Alive (9)
#15	59	F	No	Transduodenal tumor excision	1	1	1	Yes	1.4	Duodenal submucosa	2	No	II	Alive (6)
#16	41	F	Major ampulla NET, duodenal GISTs (in NF1)	Pancreaticoduodenectomy	1	2	1	No	1.4	Intrasphincteric	2	No	II	Alive (48)

*Origin of metastatic tumor from the concomitant major ampulla NET could not be excluded.
AJCC indicates American Joint Committee on Cancer; F, female; GIST, gastrointestinal stromal tumor; LVI, lymphovascular invasion; M, male; NF1, type 1 neurofibromatosis; WHO, World Health Organization.

The minor papilla/ampulla (MIPA) of the duodenum, which is generally situated 1.8 cm (1.3 to 2.5 cm) ventroproximal to the ampulla of Vater, arises at around the fourth gestational week as the point of drainage of the embryonic dorsal pancreatic duct into the duodenum.[1] During pancreatic development, the dorsal and the ventral embryonic

TABLE 2. Histologic and Immunophenotypical Features of the 16 MIPA-NETs Investigated

Case	Histologic Patterns	Psammoma Bodies	Synaptophysin	Chromogranin-A	Gastrin	Serotonin
#1	Trabecular+tubulacinar+nesting	No	Pos	Pos	Neg	Neg
#2	GP	No	Pos	Neg	Neg	Neg
#3	Tubuloacinar+nesting+trabecular	Yes	Pos	Pos	Neg	Neg
#4	Nesting+trabecular+tubuloacinar	No	Pos	Pos	Neg	Neg
#5	Tubuloacinar+nesting	Yes	Pos	Pos	Neg	Neg
#6	Nesting+trabecular+tubuloacinar	No	Pos	Pos	Neg	Neg
#7	Nesting+tubuloacinar	No	Pos	Pos	Neg	Neg
#8	GP	No	Pos	Pos	NA	Neg
#9	Tubuloacinar+nesting	No	Pos	Pos	Neg	Neg
#10	Nesting+tubuloacinar	No	Pos	Pos	Pos (30%)	Neg
#11	Tubuloacinar	Yes	Pos	Pos	Neg	Neg
#12	GP	No	Pos	Pos	Neg	Neg
#13	Tubuloacinar	No	Pos	Pos	Pos (5%)	Neg
#14	Nesting+tubuloacinar	No	Pos	Pos	Neg	Neg
#15	Tubuloacinar	Yes	Pos	Pos	Neg	Pos (30%)
#16	Tubuloacinar	Yes	Pos	Pos	Neg	Pos (5%)

*Expressed in the epithelial component.
†Scored according to Volante et al.[17]
‡Expressed in both epithelial component and ganglion-like cells.
AST indicates ampullary-type somatostatin-producing neuroendocrine tumor; CK7, cytokeratin 7; NA, not available; Neg, negative, nfNET, nonfunctioning neuroendocrine tumor; Pos, positive.

buds of the pancreas fuse at around the seventh week, and their duct systems coalesce to form the main pancreatic duct of Wirsung. A proximal portion of the dorsal bud duct commonly remains as the accessory duct of Santorini, while its connection with the duodenum is generally obliterated; however, in >40% of individuals, the accessory pancreatic duct remains patent into the duodenum through the minor papilla.[2] A nodule may form in the submucosa of the duodenum, composed of pancreatobiliary type ductal/ductular structures of the accessory pancreatic duct and residual portions of pancreatic parenchyma from the dorsal bud; amounts and type of tissue vary between individuals. These ducts are surrounded by smooth muscle bands that provide a sphincter action similar to the sphincter of Oddi at the ampulla of Vater.[3] Neuroendocrine cells are frequently found in the MIPA, often forming micronests, within the epithelium of the terminal accessory pancreatic duct or in the surrounding stroma; they predominantly consist of somatostatin-producing or pancreatic polypeptide–producing cells.[1–4]

Tumors of the MIPA region are rare and poorly defined. A variety of epithelial neoplasms have been reported to occur in the MIPA, such as adenocarcinomas,[5] intraductal papillary mucinous neoplasms,[1] and neuroendocrine tumors (NETs), including somatostatin-producing tumors and gangliocytic paragangliomas (GPs).[6–14] However, as the literature on NETs of the MIPA is limited so far to individual case reports, the pathologic profile and biologic behavior of these rare tumors are not yet well established.

The objectives of this study were as follows: (i) to analyze the clinical, pathologic, immunophenotypic, and prognostic features of a series of 16 NETs arising in the MIPA; (ii) to compare them with major ampulla and extra-ampullary duodenal NETs from our previous series,[15] and (iii) to review pertinent literature in order to improve our knowledge of these rare neoplasms.

MATERIALS AND METHODS

Pathology files and Endocrine Tumor Registers of the Anatomic Pathology Departments of Pavia, "Vita-Salute San Raffaele" (Milan), Humanitas (Milan), Padua, Genoa, and Insubria Universities, and of Catholic University of Rome were searched for surgical and endoscopic resection specimens of cases diagnosed as "neuroendocrine tumor" or "endocrine tumor" or "carcinoid" of the MIPA, diagnosed between 1980 and 2017. Only cases fulfilling the following criteria were included in this study: (a) tumor location at 1 to 3 cm proximal to the major papilla, which had to be uninvolved or independently involved by a second, histologically separate, NET and (b) histologic evidence of pancreatobiliary ducts and/or residual pancreatic acinar tissue in close association with the NET. Primary pancreatic NETs with extension to the MIPA region were excluded.

Sixteen MIPA-NETs were identified, including 2 NETs found incidentally in pancreaticoduodectomy specimens for pancreatic ductal adenocarcinoma (Table 1). Pertinent clinical, endoscopic, radiologic, and laboratory data as well as follow-up information were obtained from clinical records, local tumor registries, and interviews with family doctors. An overall median follow-up of 38 months (range: 2 to 275 mo) was recorded.

Tissue from pancreatoduodenectomy specimens was available in 11 cases and from transduodenal tumor excision/minor ampullectomy in 5 cases. All tumor samples were reviewed by 3 surgical pathologists specialized in neuroendocrine pathology (A.V., L.A., and E.S.).

Histologically, the neoplasms were studied for the following parameters: tumor differentiation, growth pattern, number of mitoses per 2 mm^2, lymphovascular invasion, tumor size, level of duodenal wall invasion, involvement of pancreas and periduodenal tissues, and

TABLE 2. (*Continued*)

Somatostatin	Pancreatic Polypeptide	MUC1	CK7	Somatostatin Receptor Type 2A†	Somatostatin Receptor Type 5†	Histotype
Pos (80%)	Neg	Pos	Neg	0	3	AST
Pos (20%)‡	Pos (30%)*	Neg	Neg	3*	NA	GP
Pos (90%)	Neg	Pos	Pos	0	3	AST
Neg	Neg	Neg	Neg	3	0	nfNET
Pos (100%)	Neg	Pos	Pos	0	3	AST
Pos (100%)	Neg	Pos	Pos	0	3	AST
Neg	Neg	Neg	Neg	3	0	nfNET
Pos (30%)‡	Pos (50%)*	Neg	NA	NA	NA	GP
Neg	Neg	Neg	Neg	2	2	nfNET
Pos (80%)	Neg	Pos	Pos	2	3	AST
Pos (100%)	Neg	Pos	Pos	0	3	AST
Pos (20%)‡	Pos (30%)*	Neg	NA	3*	3*	GP
Pos (100%)	Neg	Pos	Pos	0	0	AST
Pos (100%)	Neg	Pos	Pos	0	2	AST
Pos (60%)	Neg	Pos	Neg	2	0	AST
Pos (100%)	Neg	Pos	Pos	0	0	AST

local lymph node/distant metastases. The AJCC staging system for ampullary NETs[16] was also adopted for MIPA-NETs. Patterns of growth were recorded as nesting, trabecular, and pseudoglandular/tubuloacinar, whereas cases showing the typical 3 cell types' (paraganglioid, gangliocytoid, and sustentacular) morphology were classified as GPs.

Immunohistochemical tests were performed for Ki67 (monoclonal, clone MIB1; Dako, Carpinteria, CA), synaptophysin (monoclonal, clone snp88; BioGenex Laboratories, San Ramon, CA), chromogranin A (monoclonal, clone LK2H10; Ventana, Tucson, AR), gastrin (polyclonal; Dako), serotonin (polyclonal; Novocastra, Newcastle, UK), somatostatin (polyclonal; Dako), pancreatic polypeptide (polyclonal; Peninsula Laboratories, Belmont, CA), apomucin MUC1 (monoclonal, clone VU4H5; Santa Cruz Biotechnology, CA), cytokeratin 7 (CK7, monoclonal, clone SP52; Ventana), somatostatin receptor type 2A (monoclonal, clone UMB1; Abcam, Cambridge, UK), and somatostatin receptor type 5 (monoclonal; clone UMB4, Abcam). Somatostatin receptor expression was assessed with the scoring system proposed by Volante et al[17]; only score 2 and 3 neoplasms were regarded as positive. In cases with GP histology, immunoreaction for S100 protein (polyclonal; Dako) was also carried out.

According to the WHO 2010 criteria, NET grade was assigned on the basis of the Ki67 index and the mitotic count.[18,19] The Ki67 labelling index was assessed in accordance with ENETS/WHO recommendations; the zone of highest nuclear labelling (hot spot) was identified, and the percentage of stained tumor cells, per 2,000 neoplastic cells, was evaluated. G1 tumors were those with <2 mitoses/2 mm^2 and <3% Ki67 index, and G2 tumors were those with 2 to 20 mitoses/2 mm^2 or 3% to 20% Ki67 index. In NET cases, wherein the Ki67 index was close to the cut-offs, high magnification (×400) microphotographs of the hot spots were taken. The captured images were then analyzed manually on a printed copy.[20] No G3 NET or neuroendocrine carcinomas were identified.

For comparison, a series of major ampulla and extra-ampullary duodenal NETs not associated with hyperfunctional syndrome, taken from our previous study,[15] was reinvestigated in parallel.

The study was performed in agreement with the clinical standards laid down in the 1975 Declaration of Helsinki and its revision and was approved by the Ethics Committee of the Ospedale di Circolo, Varese, Italy (No. 0008465).

Statistical Analysis

Comparisons of patient and tumor characteristics across histotypes were made by means of Fisher exact test for categorical variables and by Mann-Whitney test for continuous variables. A 2-sided *P*-value of <0.05 was considered statistically significant. Stata 14 (StataCorp, College Station, TX) was used for computation.

RESULTS

Clinicopathologic Analysis of the 16 MIPA-NET Cases Investigated

All the 16 collected MIPA neoplasms were classified as NETs due to their well-differentiated endocrine-type histology as well as diffuse chromogranin A and/or synaptophysin immunoreactivity. Their clinicopathologic features are summarized in Table 1. The median age at diagnosis was 57.5 years, and the female-to-male ratio was 2.2:1. Although these NETs exhibited a relatively small size (median: 1.45 cm) and most (15/16, 94%) were low-grade (G1) tumors, they showed invasive potential in terms of invasion of the duodenal muscularis propria or beyond (37%), lymphovascular invasion (50%), or regional lymph node metastases (27%). Notwithstanding these characteristics, no tumor caused patient death during a median follow-up of 38 months.

No clinically relevant, hormone-mediated hyperfunctional symptoms were detected. In particular, no somatostatinoma or gastrinoma syndrome was found. Two of the MIPA-NET cases also showed a topographically separate NET in the major ampulla. Of these bi-ampullary cases, one (#16 in Tables 1, 2) arose in a patient with neurofibromatosis type 1 and the other (#10 in Tables 1, 2) in a neurofibromatosis type 1–free 31-year-old woman with early childhood polycythemia and bilateral metastatic pheochromocytoma, diagnosed and operated at the age of 13 years.

Histologic and Immunophenotypic Analysis of MIPA-NETs

Histologic and immunohistochemical findings pertinent to tumor type characterization are detailed in Table 2. Histologic structure (nesting to trabecular vs. tubuloacinar vs. GP type) and immunoreactivity for somatostatin, pancreatic polypeptide, MUC1, and somatostatin receptor type 2A proved more informative for subtype classification. It should be outlined that 10 of the 16 MIPA NETs investigated showed (a) extensive (>50%, ranging from 55% to 100% positive cells, median: 100%) somatostatin reactivity, (b) focal to extensive tubuloacinar structures, often enveloping intraluminal psammoma bodies, composed of cells with fairly abundant, finely granular cytoplasm, and basally polarized nuclei, in a background of nested/microlobular aggregates, (c) cytoplasmic and/or membranous MUC1 staining (often with positive luminal membranes and contents of acini, including psammoma bodies), and (d) absence of typical triphasic histology of GP. In keeping with previous investigations dealing with duodenal and major ampulla NETs,[15] we classified such MIPA cases as ampullary-type somatostatin-producing neuroendocrine tumors (ASTs) (Fig. 1). In 8 of the 10 AST cases, tumor cells also showed cytokeratin 7 immunoreactivity. Interestingly, no (8 cases) or limited (2 cases showing scattered cells with complete or partial membrane staining) somatostatin receptor type 2A membranous expression was found in AST cells.

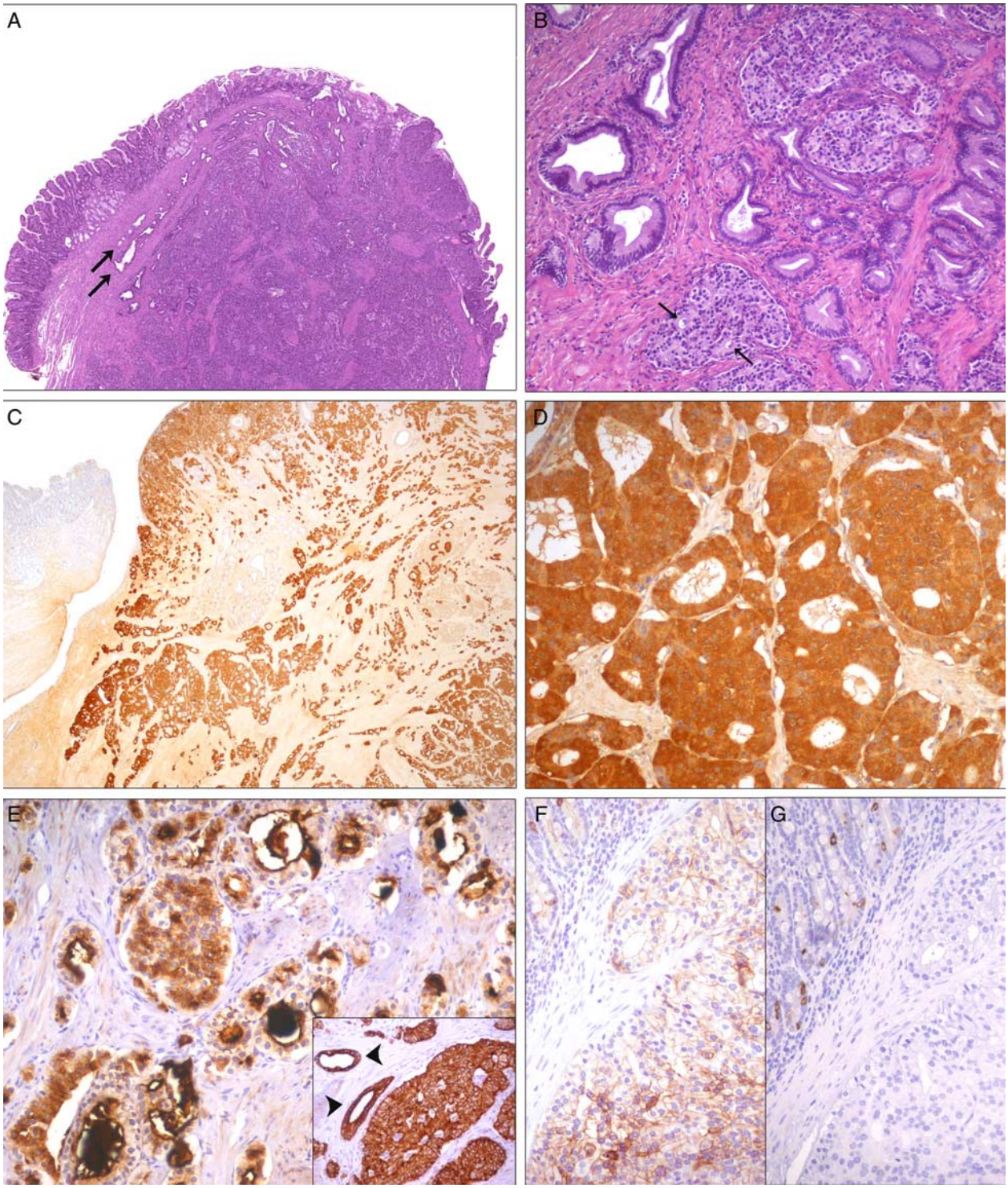

FIGURE 1. A–G, Ampullary-type somatostatin-producing NETs (ASTs) of the MIPA. A and B, (Hematoxylin and eosin) AST protruding into the duodenal lumen from the MIPA region (A); note residual MIPA ductules (thick arrows) and, in (B) inside the tumor nodules, the presence of sparse tubule-acinar structures (thin arrows). C and D, (Somatostatin immunohistochemistry) Extensive somatostatin immunoreactivity of an AST surrounding an open Santorini duct (C), showing prominent tubuloacinar pattern (D). E, MUC1 immunoreactivity of tumor cell cytoplasm, luminal border, and content of tubuloacini, as well as of well-formed psammoma bodies. In the inset, cytokeratin 7 reactivity of both AST and ampullary ductules (arrowheads). F and G, Two adjacent sections of the same AST showing tumor cell membranous reactivity for somatostatin receptor type 5 (F, somatostatin receptor type 5 immunohistochemistry) and negativity for somatostatin receptor type 2A (G, somatostatin receptor type 2A immunohistochemistry). Note, as a control, the reactivity of nontumor cells in the overlying mucosa.

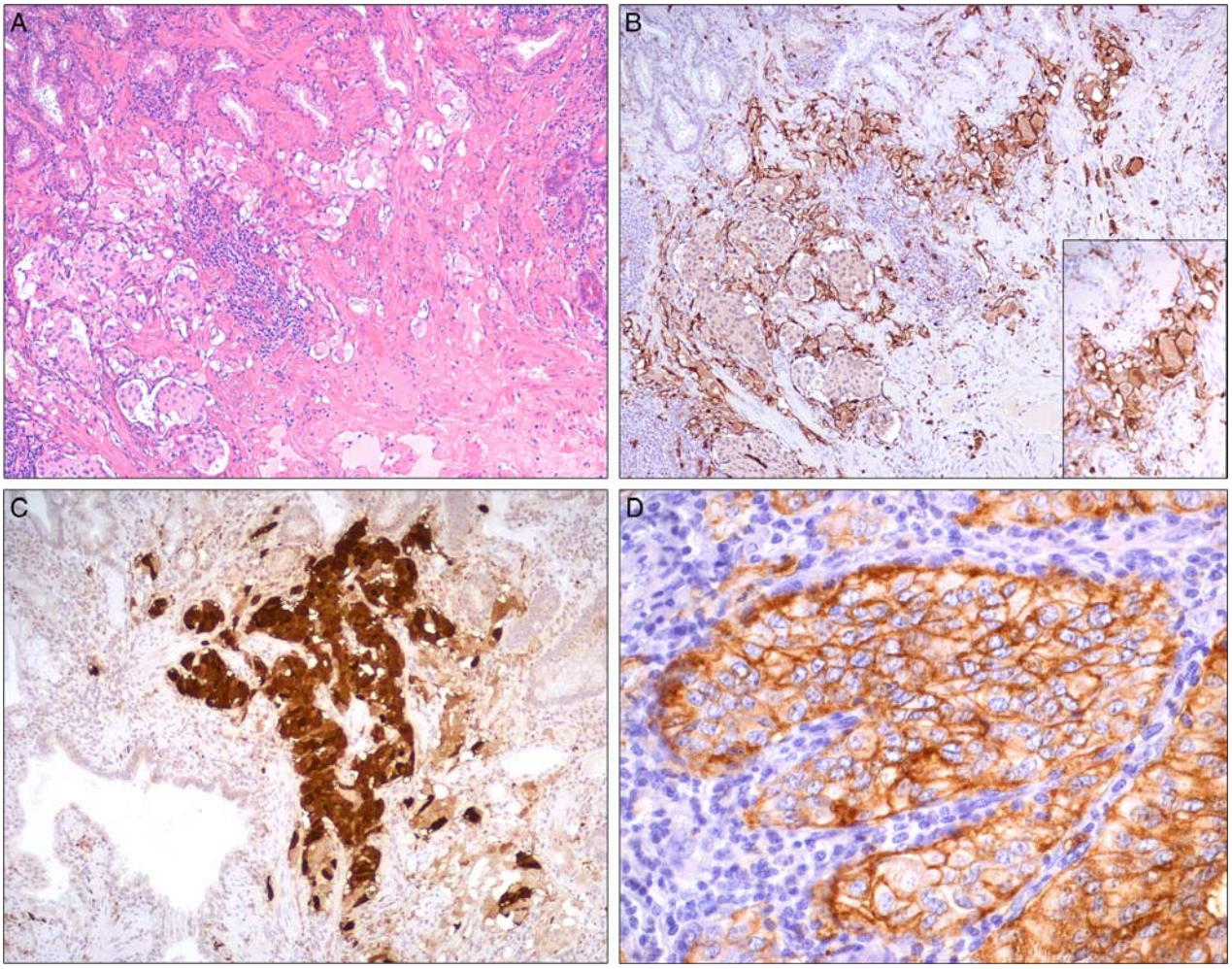

FIGURE 2. A–D, GP of the MIPA. A, Hematoxylin and eosin. B, S100 immunohistochemistry. Two sections though the same GP showing in their upper parts remnants of ampullary ductules' covering; on the deeper left, a paraganglioid growth formed by solid nests of epithelioid cells surrounded by thin S100-positive sustentacular cells. On the right, a stroma-enriched component with S100-positive spindle cells closely surrounding large ganglion-like cells, enlarged in the inset to (B). C, Epithelioid cells of the paraganglioid component are reactive for pancreatic polypeptide (pancreatic polypeptide immunohistochemistry). D, Score 3 membranous reactivity for somatostatin receptor type 2A of epithelioid cells (somatostatin receptor type 2A immunohistochemistry).

Three MIPA tumors showed the typical triphasic morphology of GP, that is, a predominance of epithelioid neuroendocrine cells forming paraganglioma-like solid micronodules, regularly demarcated by S-100 reactive supporting/sustentacular cells, coupled with a few ganglion-like cells, which were more frequently found within large, often more deeply located, fascicles, partly composed of S-100-positive spindle cells (Fig. 2). Many epithelioid cells exhibited reactivity for pancreatic polypeptide and/or somatostatin; the latter was also found in some ganglion-like cells. In addition, GP epithelioid component had score 3 somatostatin receptor type 2A immunoreactivity. No lymphoinvasion or lymph node metastases were observed in GP cases.

Three MIPA NETs escaped characterization as AST or GP, while showing predominance of trabecular or nesting structure (Fig. 3), very scarce or no reactivity for somatostatin, no reactivity for MUC1, and high expression of both type 2A and type 5 somatostatin receptors. They resembled ordinary nonfunctioning NETs commonly found in extra-ampullary duodenal mucosa.[15]

Comparison of MIPA-NETs With NETs of the Major Ampulla and the Extra-Ampullary Duodenum

In Table 3, relevant findings obtained in the 10 MIPA ASTs are summarized and compared with those of 29 corresponding major ampulla ASTs available from our previous study[15] and are, here, reinvestigated in parallel. The substantial homology in histologic, immunophenotypic, and invasive/metastatic patterns between minor and major papilla/ampulla ASTs is evident, although major ampulla

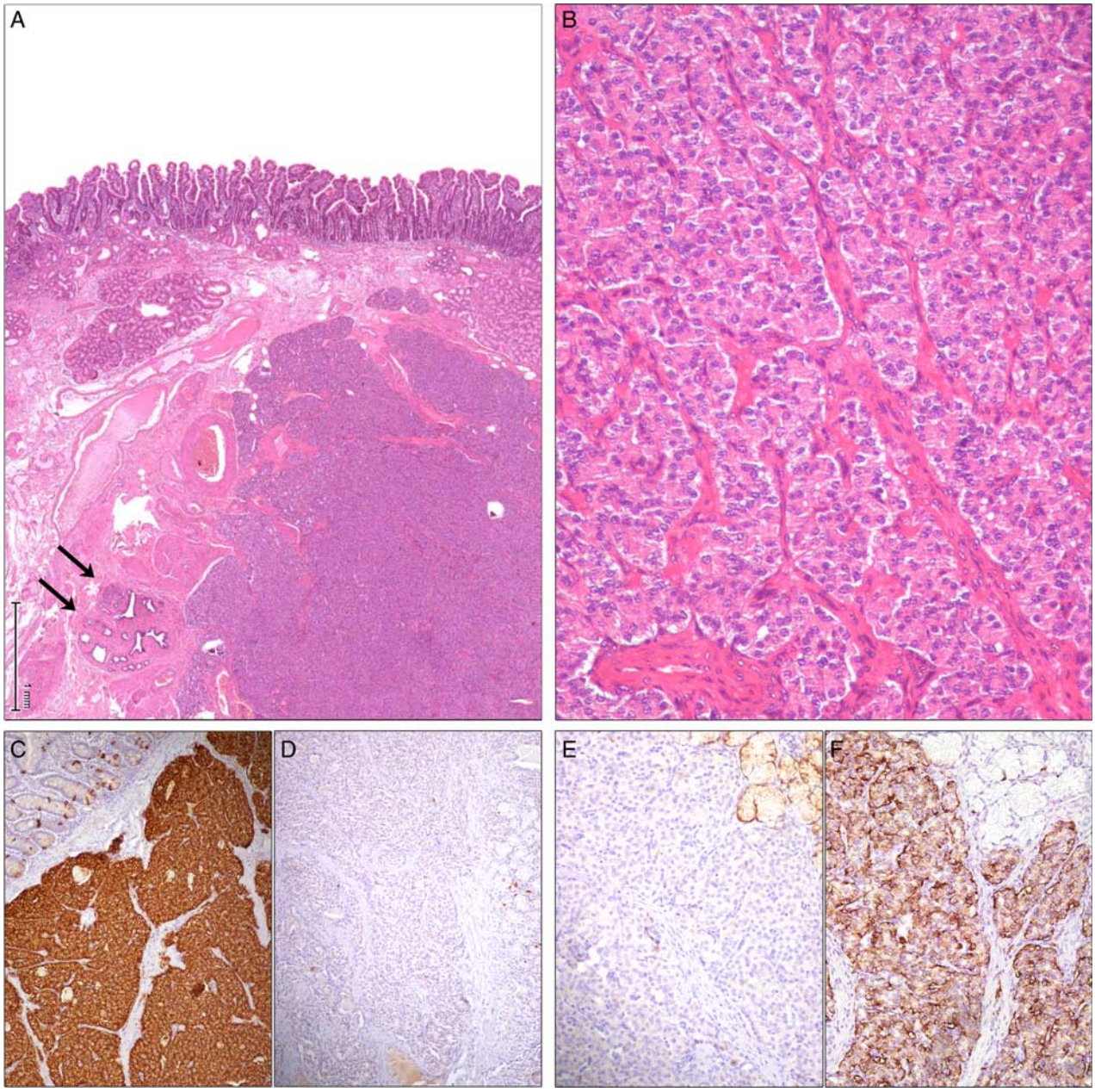

FIGURE 3. A–B, Ordinary nonfunctioning NET of the MIPA. A and B, (Hematoxylin and eosin) A well-differentiated nfNET located in the duodenal submucosa (A) adjacent to MIPA structures (arrows) and showing a nesting to trabecular pattern at higher magnification (B). Tumor cells show chromogranin-A immunoreactivity (C, chromogranin-A immunohistochemistry), while all hormones tested, including somatostatin (D, somatostatin immunohistochemistry), as well as the marker MUC1 (E, MUC1 immunohistochemistry), are negative. The same NET shows strong membranous expression of somatostatin receptor type 2A (F, somatostatin receptor type 2A immunohistochemistry).

ASTs exhibited a larger size in comparison with their MIPA counterpart ($P = 0.019$). Interestingly, both the minor and major ampulla NETs found in the neurofibromatosis type 1–associated and the pheochromocytoma-associated cases showed typical AST patterns.

The 3 MIPA NETs remaining after separation of ASTs and GPs resembled histologically and immunohistochemically a group of 9 similarly identified ordinary nonfunctioning NETs from the major ampulla. Cumulative findings of such minor plus major ampulla ordinary nonfunctioning NETs (12 cases) and comparison with those of 94 ordinary nonfunctioning NETs from the extra-ampullary duodenum are outlined in Table 3. Similarities were seen between ampullary and extra-ampullary ordinary nonfunctioning NETs concerning histologic/immunophenotypic features, although a lower

TABLE 3. Comparison of MIPA NETs With Corresponding Histotypes of the Major Ampulla and ExtraAmpullary Duodenum

				n/N (%)			
Histotype	**Site**	**No. Cases**	**Median Age (y)**	**Somatostatin ≥1%**	**Somatostatin >50%**	**Tubuloacinar Structures**	**Psammoma Bodies**
AST	MIPA	10	57.5	10/10 (100)	10/10 (100)	10/10 (100)	5/10 (50)
	Major ampulla	29	50	29/29 (100)	29/29 (100)	29/29 (100)	11/29 (38)
	Total	41*	50	41/41 (100)	41/41 (100)	41/41 (100)	17/41 (41)
Ordinary nfNETs	Ampullary (MIPA + major)	12†	58	1/12 (8)	0/12 (0)	3/12 (25)	0/12 (0)
	Nonampullary duodenal	94	65	31/81 (38)	6/81 (7)	3/94 (4)	0/94 (0)
	Total	106	64	32/93 (34)	6/93 (6)	6/106 (6)	0/106 (0)

Significant differences by Fisher exact test: ASTs (as a whole) versus nfNETs as a whole or ampullary nfNETs or non–ampullary-duodenal nfNETs: $P<0.001$ for somatostatin ≥1% or >50%, tubuloacinar structures, psammoma bodies, MUC1, and somatostatin receptor type 2A; ASTs versus nfNETs as a whole or nonampullary nfNETs: $P<0.001$ for size >1 cm, invasion of muscularis propria or beyond and lymph node metastasis; ASTs versus nonampullary duodenal nfNETs: $P<0.001$ for gastrin; ASTs versus ampullary nfNETs: $P=0.008$ for size >1 cm. Significant differences by Mann-Whitney test: ASTs versus nfNETs as a whole or non–ampullary-duodenal nfNETs: $P<0.001$ for age at diagnosis and size; ASTs versus ampullary nfNETs: $P=0.003$ for size; MIPA ASTs versus major ampulla ASTs: $P=0.012$ for size.

*Including 2 previously characterized extra-ampullary ASTs.

†Nine from major ampulla and 3 from MIPA.

nfNET indicates nonfunctioning neuroendocrine tumor.

rate of gastrin expression ($P<0.001$) and an increased invasive potential ($P=0.024$) appeared among the ampullary cases. On the contrary, highly significant (mostly $P<0.001$, Fisher exact test) differences were found between ordinary nonfunctioning NETs as a whole and ASTs as a whole concerning size, histologic

TABLE 4. Review of 30 MIPA-NETs from the literature

References	**Age (y)**	**Sex**	**NF1**	**Pancreas Divisum**	**Concomitant Major Ampulla NET**	**Treatment**	**Tumor Size (cm)**	**Level of Invasion**
Malone et al[6]	46	M				Transduodenal tumor excision	0.7	
Stömmer et al[7] (case 2)	56	M		Yes		Pancreaticoduodenectomy	0.3	Duodenal submucosa
Lowes et al[8] (case 4)	50	F		Yes		Pancreaticoduodenectomy	1-2	
Borobia et al[9]	46	F	Yes		Yes	Minor ampullectomy		
Nakamura et al[11]	66	M		No		Endoscopic excision	1.2	Duodenal submucosa
House et al[10]	61	F		Yes		Pancreaticoduodenectomy	0.8	
House et al[10]	71	M		Yes		Pancreaticoduodenectomy	1.6	
Singh et al[21]	35	F		Yes		Transduodenal tumor excision	1.0	Duodenal submucosa
Outtas et al[22]	45	F		Yes		Pancreaticoduodenectomy	0.6	Intrasphincteric
Wang et al[23]	50	M				Transduodenal tumor excision	0.9	Duodenal submucosa
Waisberg et al[24]	57	F		Yes		Pancreaticoduodenectomy	2.7	
Itoi et al[25]	65	M		No		Endoscopic excision	1.2	
Bettini et al[12]	47	M	Yes		Yes	Pancreaticoduodenectomy	1.2	
Loew et al[13]	66	M		Yes		Endoscopic excision	2.0	Duodenal submucosa
Pedicone et al[26] (case 4)	40	M				Pancreaticoduodenectomy	2.0	
Kim et al[27]	56	F		Yes		Pancreaticoduodenectomy	1.2	
Fiscaletti et al[28]	61	M				Pancreaticoduodenectomy	1.5	
Nicolás-Pérez et al[29]	80	F				Endoscopic excision	1.2	Duodenal submucosa
Ha et al[30]	55	F				Pancreaticoduodenectomy	2.2	Duodenal submucosa
Maruyama et al[31]	52	M				Pancreaticoduodenectomy	1.3	
Fukami et al[32]	71	M				Pancreaticoduodenectomy	1.2	Muscularis propria
Oller et al[33]	26	M	Yes		Yes	Endoscopic excision	1.3	Muscularis propria
Aktas et al[34]	77	M				Pancreaticoduodenectomy	1.2	Duodenal submucosa
Barresi et al[35]	61	F	Yes	Yes		None		
Bhandari et al[36]	50	F	Yes	Yes		Transduodenal tumor excision	1.7	
Jara Letelier et al[37]	60	F				Endoscopic excision	2.0	
Virgilio et al[38]	59	M				Pancreaticoduodenectomy	2.5	
Matsubayashi et al[14]	71	M				Transduodenal tumor excision	1.8	Duodenal submucosa
Zandomeni et al[39]	46	F	Yes		Yes	Pancreaticoduodenectomy	1.2	Pancreas
Seo et al[40]	42	F			Yes	Endoscopic excision	1.2	Duodenal submucosa

*Proposed by the Authors of the present study and based on figures and descriptions reported in the original papers.

†Origin of concomitant major ampulla NET not excluded.

‡Coupled with superficial adenomatous polyp.

AFD indicates alive and free of disease; DOC, died of other cause; F, female; M, male; N, nesting; NF1, neurofibromatosis type 1; nfNET, ordinary nonfunctioning neuroendocrine tumor; PB, psammoma bodies; TA, tubuloacinar; TR, trabecular.

TABLE 3. (*Continued*)

n/N (%)							
MUC1+	Somatostatin Receptor Type 2A Score 2/3	Gastrin+	G2	Size > 1 cm	Size (Median) (cm)	Invasion of Muscularis Propria or Beyond	Lymph Node Metastasis
10/10 (100)	2/10 (20)	2/10 (10)	1/10 (10)	8/10 (80)	1.5	4/10 (40)	4/9 (44)
25/25 (100)	4/22 (18)	6/29 (21)	11/29 (38)	25/29 (86)	2.5	19/27 (70)	15/29 (52)
37/37 (100)	6/34 (18)	8/41 (19)	12/41 (29)	34/41 (83)	2.0	24/39 (61)	20/40 (50)
1/8 (12)	8/8 (100)	1/11 (9)	5/12 (42)	5/12 (42)	1.0	6/12 (50)	4/12 (33)
13/44 (29)	35/39 (90)	61/85 (72)	13/94 (14)	25/93 (27)	0.6	17/91 (17)	14/91 (15)
14/52 (27)	43/47 (91)	62/96 (65)	18/106 (17)	30/105 (29)	0.6	23/103 (22)	18/103 (17)

structure, invasive and metastatic patterns, and MUC1 or type 2A somatostatin receptor expression (Table 3).

Among extra-ampullary ordinary nonfunctioning NETs, we identified 31 cases showing ≥1% of somatostatin-expressing tumor cells. They showed no difference in terms of either histologic/immunohistochemical findings or invasive patterns with respect to their somatostatin-negative counterpart, while retaining significant differences com-

TABLE 4. (*Continued*)

References	Lymph Node Metastasis	AJCC Stage	WHO Grade	Histologic Pattern	Somatostatin	Status at Last Follow-up (mo)	Tumor Histotype*
Malone et al[6]	Unknown	x		N+TR+TA	Pos	AFD (16)	AST
Stömmer et al[7] (case 2)	No	II		TR+TA	Pos		AST
Lowes et al[8] (case 4)	Yes	III			Pos		Suggestive for AST
Borobia et al[9]	No	x		N+TA	Pos	AFD (36)	AST
Nakamura et al[11]	Unknown	x		GP	Pos	AFD (24)	GP
House et al[10]	Yes	III		N+TA	Pos		Suggestive for AST
House et al[10]	Yes	III		N+TA	Pos		Suggestive for AST
Singh et al[21]	Unknown	x				AFD (6)	
Outtas et al[22]	No	I					
Wang et al[23]	Unknown	x		N+TA		AFD (36)	Suggestive for AST
Waisberg et al[24]	No	II		N+TA	Pos	DOC (1)	Suggestive for AST
Itoi et al[25]	No	II				AFD (48)	
Bettini et al[12]	Yes†	III†	1		Pos	AFD (16)	Suggestive for AST
Loew et al[13]	No	II		GP		AFD (24)	GP
Pedicone et al[26] (case 4)	Yes	III	1		Neg	AFD (131)	Possible nfNET
Kim et al[27]	Yes	III		N+TA		AFD (12)	Suggestive for AST
Fiscaletti et al[28]	Yes	III		GP		AFD (12)	GP
Nicolás-Pérez et al[29]	Unknown	x		N+TA			Suggestive for AST
Ha et al[30]	No	II		TA+PB		AFD (6)	Suggestive for AST
Maruyama et al[31]	Yes	III				AFD (62)	
Fukami et al[32]	Yes	III	1				
Oller et al[33]	No	II		TA+PB		AFD (14)	Suggestive for AST
Aktas et al[34]	No	II				AFD	
Barresi et al[35]	Unknown	x		TR+TA	Pos		Suggestive for AST‡
Bhandari et al[36]	No	II	1	TA+PB	Pos	AFD (6)	AST
Jara Letelier et al[37]	No	II	1		Pos		Suggestive for AST
Virgilio et al[38]	Yes	III	1			AFD (13)	
Matsubayashi et al[14]	No	II	1	GP		AFD (67)	GP
Zandomeni et al[39]	Yes†	III†	2	TA+N		AFD (120)	Suggestive for AST
Seo et al[40]	No	II	1	TA		AFD (16)	Suggestive for AST

pared with the 41 ASTs ($P < 0.001$ for age at NET diagnosis, tumor size, rate of invasion of muscularis propria or beyond, MUC1, somatostatin receptor type 2A or gastrin expression; $P = 0.001$ for local lymph node metastasis). Notably, 6 extra-ampullary ordinary nonfunctioning NETs showed extensive (> 50% of tumor cells, median: 75%) somatostatin expression; however, none of them fulfilled all the other criteria (see above) for AST diagnosis. Thus, they were classified as ordinary nonfunctioning NETs despite extensive somatostatin expression. Worth noting, most (90%) extra-ampullary ordinary nonfunctioning NETs tested showed membranous expression of somatostatin receptor type 2A, compared with only 18% of ASTs (Table 3).

DISCUSSION

From this analysis, it clearly appears that the MIPA region is a site for primary NETs, which closely resemble those known to arise in the major papilla/ampulla. We reviewed the pertinent literature,[6–14,21–40] and we identified a total of 30 published cases (Table 4), in addition to the 16 described in this paper. Considering all 46 cases together, the tumors showed a slight female predominance (male to female ratio: 0.84), while the median age at the time of diagnosis was 56 years. The median tumor size was 1.3 cm, and the vast majority (23/25 cases with available grade information) were G1. Lymph node metastases were present in about one third of cases (13/38 cases wherein the lymph node status was reported). No MIPA-NET case had evidence of distant metastases at first diagnosis, and no patient with available follow-up (including those having undergone more conservative local interventions, such as transduodenal tumor excision, minor ampullectomy, or endoscopic resection) had tumor-related death, suggesting that MIPA-NETs generally display a relatively indolent behavior.

The complex rearrangements to which both terminal pancreatic ducts and their duodenal orifices are known to undergo during embryonic development may have a role in the genesis of some of such NETs. Indeed, a dysontogenetic origin of GP has been previously suggested,[41,42] while the frequent association of MIPA NETs with pancreas divisum (in 11/30 cases from the literature) may be pathogenetically relevant. Neurofibromatosis type 1 is known to be a common predisposing condition for both major ampulla (at least 50 cases reported) and MIPA NETs (at least 7 cases, including case #16 of Table 3).[9,12,15,33,35,36,39,43–49] The fact that all but 2 of the 7 neurofibromatosis type 1–associated MIPA cases also showed a histologically separate, concomitant major ampulla NET points to the involvement of shared, site-specific, pathogenetic factors in NET development by the 2 duodenal papillae/ampullae. No duodenal "somatostatinoma" as a component of the Pacak-Zhuang syndrome has been as yet reported within MIPA.[50,51] The pheochromocytoma-associated double minor and major ampulla AST here described (case #10) partly mimics this syndrome and will therefore be investigated further.

Similarly to a previous ampullary-duodenal NET series,[15] in the presently investigated 16 MIPA-NET cases, 3 histotypes were identified: (a) AST or ampullary-type somatostatin-producing NET (10 cases); (b) GP (3 cases), with a distinctive histology displaying 3 cellular components; and (c) ordinary nonfunctioning NET (3 cases). Careful review of the literature cases allowed us to tentatively recognize the above 3 histotypes also in most of the reported MIPA-NETs. Indeed, among the 30 MIPA-reported NETs, 4 well-documented GPs and 4 *bona fide* ASTs could be easily recognized (Table 4), in addition to at least 14 cases with features, such as extensive somatostatin immunoreactivity and/or frankly glandular/tubuloacinar histology, suggestive of AST diagnosis. Unfortunately, the lack of somatostatin immunohistochemistry and of sufficiently informative histology prevented interpretation of the remaining cases.

Special care should be paid not to misinterpret gland-forming ASTs as adenocarcinomas, also considering their wide reactivity for MUC1 and cytokeratin 7, 2 markers commonly expressed by ampullary, nonampullary duodenal and pancreato-biliary adenocarcinomas,[5,52,53] while being unusual among gastroenteropancreatic NETs.[15,54] This peculiar phenotypic behavior further outlines the need to separate ASTs from ordinary nonfunctioning NETs. It should also be stressed that, despite their propensity for local invasion and frequent lymph node metastases, none of our 16 cases, nor those from the literature, caused patient death, and this is a very different behavior compared with adenocarcinomas of the ampullary region.[52]

It should be outlined that only few cases among duodenal extra-ampullary ordinary nonfunctioning NETs (6/81 cases) showed predominance of somatostatin-expressing cells and that none of them fulfilled all of the histologic criteria of AST. The substantial restriction we observed of AST and GP to both ampullary regions should be compared with the largely extra-ampullary origin of ordinary nonfunctioning NETs. This preferential topography may also have clinical implications considering that ampullary versus nonampullary duodenal tumors require different diagnostic and therapeutic procedures.[31,55,56] Furthermore, the significantly higher invasive and nodal metastatic potential of ASTs in comparison with ordinary nonfunctioning NETs or GPs is remarkable. In addition, histotype-related differences in somatostatin receptor type 2A membranous expression, usually weak or absent in ASTs compared with GPs and ordinary nonfunctioning NETs, despite their similar high expression of somatostatin receptor type 5, might be relevant when considering somatostatin receptor-based nuclear imaging as a diagnostic approach[55,56] and somatostatin analogues as medical therapy.[57,58]

In conclusion, MIPA is a site for NETs closely resembling their major ampulla counterparts. Within both the major and minor papillae/ampullae, ASTs represent the predominant histotype, followed by the rarer GPs and ordinary nonfunctioning NETs (the latter occurring much more frequently in the extra-ampullary duodenum). Such NET subtypes differ significantly between each other, a finding of potential interest when choosing the most appropriate diagnostic and therapeutic approaches.

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